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SOME PARALLEL FINDINGS IN SCHIZOPHRENIC PATIENTS AND SEROTONIN-DEPLETED CATS

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INTRODUCTION

The possibility that the findings of sleep research might be fruitfully applied to the problems of mental illness continues to inspire countless nocturnal vigils. In this presentation, we will summarize some results obtained from all-night recordings in schizophrenic patients and some related studies in experimental animals which may enable us to suggest that REM sleep mechanisms play a role in the pathogenesis of the psychotic state.

It has always been an attractive hypothesis that the processes underlying the production of dreams may also be involved in the genesis of psychotic illnesses simply because of the obvious phenomenological similarities[1-3]. Without claiming absolute veridicality, some of the features that characterize both dreaming and psychosis may be mentioned for the purpose of illustrating this principle. Thus, hallucinations or perceptions without a basis in reality may occur in both conditions. There is often a sense of depersonalization in that the self may be observed as though events were happening in the life of someone else. Time sense may be altered so that there is a feeling of timelessness - that time has stopped - or that it has speeded up or slowed down. Feelings or affects are more variable in intensity than in waking life and may be, at times, quite inappropriate to what is going on. Objects or other people often seem to be either incompletely recognized or incompletely represented, and may be involved in episodes that would not occur in normal circumstances. At times, thinking has a bizarre, fractured quality. Judgment may be partially suspended so that events which have an aura of strangeness are believed.

The possibility of a relationship between dreaming and psychosis has become even more attractive since it has become known that dreaming is but one

aspect of a unique biological process universally distributed among all mammals, a process with its own neuroanatomical substrate and biochemical regulatory mechanism[4,5,6,7]. Thus, although many factors obviously contribute to the schizophrenic psychosis, we now know that some of the most puzzling manifestations of this illness are also the normal by-products of a functional process in the brain and are routinely generated during its regularly occurring periods of activity every night in every human being. If we can, at least for the purposes of argument, assume that there is a correspondence between dreaming, REM sleep, and some of the psychotic symptoms such as hallucinations, then we might consider the quantity and universality of REM sleep and its urgent response to deprivation, and suggest that the major puzzle nowadays is not why or how hallucinations and other symptoms occur, but rather why they don't occur. In other words, what is it that so effectively prevents most people from "dreaming while awake"? From this point of view, certain aspects of the schizophrenic psychosis could be seen as the result of a malfunction in whatever process ordinarily confines dream experiences to the obscurity and safety of sleep. Recent work in our laboratories[8,9,10,11] has suggested that such a malfunction, or something close to it, can be produced in experimental animals by the chronic administration of para-chlorophenylalanine (PCPA), a selective depletor of brain serotonin[12]. The degree of relevance that such a "preparation" might have for those interested in the psychotic state in humans will be left to individual judgment. Our task in this presentation will be merely to summarize pertinent experimental data in both conditions and to point out the intriguing correspondences that this data has revealed.

Before proceeding further, we must define an important distinction with regard to the physiological concomitants of REM sleep. These concomitants may be divided into two classes which have been termed phasic events and tonic events[13,14]. Tonic events are those changes or physiological characteristics which more or less define the REM period, and which are maintained continuously throughout its duration. Examples of tonic events would be EEG activation, EMG suppression, brain temperature elevation, etc. Phasic events are those activities which are short-lasting and discontinuous. In addition to rapid eye movements themselves, a number of other activities have been described that fall into this category - for example, middle ear muscle contractions, cardiovascular irregularities, respiratory chances, muscular twitching, phasic changes in pupil diameter, phasic fluctuations in penile tumescence, and finally, the unique bursts of monophasic sharp waves that characterize the electrical activity of the pons oculomotor nuclei, lateral geniculate nuclei, and visual cortices[15,16,17].

It is our feeling that these monophasic sharp waves, hereafter referred to as PGO (pontine-geniculate-occipital) spikes, represent some sort of primary triggering process for all other phasic events, particularly eye movements. Attesting to their primacy in the triggering of phasic events in general is the fact that PGO spikes nearly always appear some time before the actual onset of the REM period. This and other properties of PGO spikes are illustrated in Figures 1 and 2.

Besides being a helpful taxonomic refinement, the distinction between tonic events and phasic events is important because under certain conditions, these two classes of activity may be dissociated. The first clear-cut demonstration of such a dissociation was accomplished by Delorme and Jouvet[18];

who showed that REM periods were abolished by high doses of reserpine in the cat, but that phasic events (PGO spikes) continued to discharge throughout the period of suppression. An important principle is suggested by these and similar results, to wit: that at least two distinct neurological systems and/or mechanisms are involved in the REM phenomenon - the first a system which functions to produce REM periods, in effect a tonic events system; and the second, a system which generates or triggers the phasic events.

Finally, if we had to make a choice, it would seem that the subjective experience associated with REM periods should also be classified as a kind of phasic activity. The fact that some dream experiences appear to take place in NREM sleep[19,20,21] is not contradictory since a portion of the PGO spike activity is also associated with this phase of the sleep cycle.

THE EFFECT OF CHRONIC PCPA ADMINISTRATION IN CATS

A theory regarding the function of serotonin in brain has been developed by Jouvet[6,22,23,24] in which the amine is viewed as thetransmitter or neuromodulator substance of a NREM sleep-inducing system whose cell bodies lie in the raphé system, a group of nine midline cellular aggregations extending from the medulla oblongata to the posterior diencephalon. Recent studies utilizing fluorescence microscopy have demonstrated that nearly all the serotonergic neurons of the brain are located in these nuclei and that serotonin in other portions of the brain lies mainly in the axonal terminals of raphé neurons[25,26]. In an extensive series of ablation experiments in cats, Jouvet found that loss of raphe tissue was associated with the development of insomnia which, in turn, was correlated with a fall in brain serotonin. This result was buttressed by the additional finding that depletion of serotonin by administration of PCPA also produced a drastic reduction in sleep time. Finally, it

was noted that both PCPA and lesions in the raphé system were followed by the appearance of PGO spikes in the waking state.

We have confirmed and extended these results with PCPA and have been led to a somewhat different notion about the role of serotonin in brain[8,9,10,11,27]. Our studies involved continuous polygraphic and behavioral observations of cats, 24 hours a day, 7 days a week, for long periods of time, up to two or more months. The mean normative values for PGO spike densities in REM periods as well as daily NREM and REM sleep times were first established during extended baseline periods. The polygraphic observations together with extensive behavioral observation and behavioral testing were continued throughout the subsequent period of chronic PCPA administration during which each cat received daily subcutaneous injections of the drug in doses ranging from 75mg/kilo to 300mg/kilo.

Very little change was noted during the first 48 hours of PCPA administration. However, at some specific point in time, monophasic sharp waves bearing an exact resemblance to PGO spikes began to appear during wakefulness in every cat. The development of this particular change is illustrated in Figure 3. Nearly all other important changes seemed to occur in close association with the appearance of spike activity in the waking animal. There was a precipitous drop in sleep time (both REM and NREM fractions) and one had the impression of a profound internal disturbance. Indeed, the animals often seemed to respond to the internally generated bursts of PGO spike activity as if they were external stimuli. These responses most frequently took the form of alerting and very often included searching movements of the head and eyes. Occasionally, the behavior associated with bursts of spikes suggested the possibility of fullblown hallucinations. In addition to the development of insomnia and "hallucinations," the PCPA animals underwent a profound and previously undescribed behavioral change which included the emergence of

hypersexuality, hyperphagia, profound irritability, as well as a number of alterations peculiar to individual animals. These changes were exceedingly dramatic and it is difficulty to do them justice with more words. For example, previously indifferent male cats would not only compulsively mount anesthetized male cats and passive male cats, but also would relentlessly stalk a fully awake, raging, clawing normal tomcat with sexual intent for as long as we would allow. Cats who normally ignored laboratory rats began to kill them with a rapidity and concentrated savagery that evoked images of the jungle. A good analogy to the emergence of these behavioral and electrophysiological changes in association with PCPA administration is the flood produced by destroying a dam. In this instance, the dam might be the serotonergic neurons of the raphé system.

Although the fullblown PCPA effect took several days to devdlop (which may simply represent the time required to reach a critical threshold of serotonin depletion), a nearly instantaneous reversal of both the electrophysiological and behavioral changes was accomplished by administering very small amounts of 5-hydroxytryptophan, the metabolic precursor of serotonin.

After several days in the state of insomnia and drive accentuation described above, a reversal of varying degrees took placeeven though the PCPA dosage was always maintained. The animals became more and more lethargic and sleep periods were both longer and more frequent. PGO spike bursts were less intense and appeared to lose their power to disturb the animal. By the seventh or eighth day of PCPA administration, both NREM and REM sleep times had returned to maximum values which were often within the baseline range. Figure 4 illustrates a typical sequence in one cat.

Interesting changes took place in the pattern of PGO spike discharge. When the spikes appeared in the waking state, the frequency within REM periods showed a rapid fall to a substantially lower value in all cats (see Figure 5). Initially, only occasional spikes were seen in the waking state, but the frequency increased very quickly to a plateau which was always less than the discharge rate within REM periods. PGO spikes began to occur almost continuously in NREM sleep - that is, there were no prolonged periods of NREM sleep without spikes. As the PCPA treatment continued, it was as if all regulation of PGO activity had vanished allowing the spike discharge to disperse itself more or less equally regardless of background state.

We maintained cats on PCPA for up to 37 days. When the drug was withdrawn, there was a gradual return to normalcy over a three to five day period.

REM SLEEP DEPRIVATION STUDIES IN SCHIZOPHRENIC PATIENTS

A number of studies have described the all-night sleep patterns of various populations of schizophrenic patients[28-35]. Although there has been little consistency among the studies with regard to therapy (drug administration), diagnosis, and clinical state, there have been a few reasonably consistent, if somewhat undramatic, findings in what are otherwise essentially normal data. The first finding is that the schizophrenic populations appear to have a shorter latency for the onset of the first REM period compared to most normal control groups. Secondly, the overall sleep patterns of schizophrenics appear to be significantly unstable in that the NREM-REM cycle is extremely variable in length and the various sleep stages appear to be easily and frequently interrupted. In addition, the overall amounts of time devoted to the different stages appear to be highly variable from patient to patient.

In our own work[36,37,38,39], we have attempted to reduce some of the confounding variables by keeping phenothiazine medications constant throughout the periods of study and by carefully delineating the clinical state of the patient population. Our observations have been focused on two groups. Both groups were composed of chronic process schizophrenics with evidence of deterioration in occupational and social functioning. The patients in one group were experiencing active symptomatology - hallucinations, delusions, thought disorder, bizarre motor activity, and affective abnormalities. The continuing symptomatology was accepted by these men and served to explain their position in life for them. This was probably a factor that mitigated anxiety. The second group was as clinically differentiated as possible, consisting of patients with no active symptomatology whatsoever. In other words, they appeared to be in complete remission. These two patient populations were subjected to two consecutive nights of selective REM sleep deprivation. Each patient had baseline, deprivation, and recovery recordings.

Nine patients were studied in the actively ill group, and all nine failed to show a post-deprivation rise in total REM sleep time (REM rebound). Over the entire five night recovery period, they averaged only a 5 percent make-up of the REM time lost on the two deprivation nights. One patient was also REM deprived for an extended period of eight consecutive nights and he too failed to show the usual compensatory REM rebound.

On the other hand, patients in remission, including some patients who had also been studied while actively ill, all showed substantial rebounds averaging over 200 percent makeup following the deprivation. The percent makeup can be contracted to the 50%-60% level characteristic of normal subjects, or non-schizophrenic patient control subjects over a five night recovery period following two deprivation nights. None of the patients showed any increase

in symptomatology during or after the deprivation periods. In a related study, Luby and Caldwell[40] failed to see either an immediate or a delayed REM sleep rebound following a period of total sleep deprivation in a group of chronic schizophrenics.

There are only two other reported studies of selective REM sleep deprivation in schizophrenics. In one, Akumi et al.[41] found little or no REM rebound during recovery sleep following three nights of deprivation in three patients. However, in the other study, Vogel and Traub[42] obtained substantial REM sleep rebounds following five to seven nights of selective REM sleep deprivation in five schizophrenic patients. These patients were described as follows:

"In the last few years, all subjects had several acute episodes of floridly psychotic symptoms which included delusions, assaultive behavior, auditory and visual hallucinations, fecal smearing, catatonia, and word salad speech. During the baseline period of the experiment, the subjects were free of these florid symptoms." A variety of tests were repeatedly administered to the patients to help define their clinical state at different times during the experimental period. REM deprivation produced no change on the tests, but the initial levels or scores were not reported by Vogel and Traub. It seems to us that their patients were more similar to the patients in our second group who were essentially in complete remission with no active symptomatology. Accordingly, the observation of REM rebounds by Vogel and Traub is consistent with the observations reported by us on this second group.

In terms of a possible obligatory "quota" of REM sleep, we have considered the failure to rebound in actively ill patients a finding of great importance with far-reaching implications for understanding the actively psychotic state. In view of this, we have aimed our studies in experimental

animals (see earlier sections) toward the goal of producing a laboratory model of the clinical situation and reproducing as many of the clinical findings as possible. In this sense, and in this sense only, we have regarded the cat treated chronically with PCPA as a laboratory model of the psychotic state.

SPECIFIC PARALLELS BETWEEN CHRONIC PCPA CATS AND SCHIZOPHRENIC PATIENTS

There is a great deal of resistance to the concept of "psychosis" in experimental animals, particularly in non-primate species. This is presumably because so many aspects of psychotic illnesses, indeed the essential defining characteristics, involve disturbances of functions that are uniquely human - such as symbol formation, associative processes, language and communication. On the other hand, these overt symptoms occupy the exclusive focus of our attention only because we have no information that definitely implicates changes on other levels of function. If we are willing to assume - at least for the sake of argument - that the presence of a biochemical abnormality is a necessary factor in the pathogenesis of the schizophrenic psychosis, it shall then be completely obvious that reproducing the exact same biochemical abnormality in an experimental animal, such as the dog, cat, or rat, would never give us a condition resembling the human illness in all respects. The important question is, if we knew the basic cause of schizophrenia (recognizing, of course, the possibility of multiple causes and multiple syndromes) and could reproduce it in an animal, what would we get? First of all, we might get nothing. A biochemical defect that would produce schizophrenia in a human might have no significant consequence for a rat, or even a monkey. The best one could hope is that any disturbances seen in experimental animals

would be recognizable members of the schizophrenic syndrome (inappropriate emotional behavior would be an example), and that no changes would be totally unrelated.

If we really knew the basic cause of schizophrenia, the foregoing discussion would be academic. No one would care the least whether or not reproducing the basic abnormality in experimental animals also reproduced the clinical syndrome. All our interest and concern would be directed toward reversal. Behavioral change would be of interest only if an independent measure of such a reversal were needed. Unfortunately, we know nothing about the basic cause of schizophrenia, or at least very little, and we are still searching for a good prospect. For this reason alone, while recognizing the many difficulties and logical inconsistencies, we cannot afford to ignore any experimentally produced change in animals that bears a reasonable resemblance to the schizophrenic syndrome or any of its parts. At the moment, the promise of such a resemblance - its relevance - can be judged only on the basis of whatever demonstrable physiological and behavioral parallels are present.

It is from this point of view that we would like to describe some intriguing similarities between the chronic PCPA syndrome in the cat and the schizophrenic psychosis in the human. We will judge this endeavor worthwhile if it stimulates any further attempt to evaluate the functional status of serotonergic systems in patients or any new approaches to the problem of measurement. Whether or not the chronic PCPA cat is the best model, or even a good model, has little meaning since, as far as we know, in the whole realm of experimental psychopathology there is no other condition or preparation that has been advanced as an animal model of the schizophrenic psychosis.

Before proceeding further, we should mention one possible parallelism which cannot be conclusively evaluated at the present time, but which we do not think exists. Biochemical analysis of brain tissue from cats receiving 150mg/kilo per day of PCPA has revealed that brain serotonin falls to undetectable levels within five days and remains undetectable throughout the period of drug administration. The maximum period of treatment in our cats was 37 days. We do not believe that comparable results would be uniformly obtained if schizophrenic brains were available for analysis. The basic abnormality in the PCPA cat may be defined or conceptualized as a functional ablation of the serotonergic neurons of the raphe system, since we assumed that chronic serotonin depletion of this magnitude must interfere with normal transmission in these neurons. Accordingly, if the PCPA cat was the true and valid model of the schizophrenic psychosis, we would expect to find abnormal function of serotonin neurons in all patients, but we could not predict the specific defect. A number of possibilities exist including abnormal synthesis of false transmitters, abnormal release, abnormal receptor sites, etc., any one of which could probably produce the required functional deficit in serotonergic neurons.

1. Overall sleep patterns in PCPA cats and schizophrenic patients.

It is not the purpose of this discussion to evaluate the role of serotonin in the regulation of sleep per se, although there can be little doubt that such a role does exist. However, one issue must be clarified. The excellent and extensive work of Jouvet as well as others[43,44,45] has led some people to conclude that without serotonin there can be no sleep. Since schizophrenic patients seem, for the most part, to obtain essentially normal amounts of sleep, a serotonin depletion model in any species would be immediately suspect.

The answer to this objection is twofold. In the first place, in the hands of some investigators, PCPA has been administered without producing insomnia[46,47], and in the second place, the studies showing that selective serotonin depletion leads to insomnia all involve single doses or very limited periods of treatment with PCPA. We believe that our own studies involving prolonged treatment with PCPA in cats have satisfactorily resolved any apparent conflict among other investigators. All of our cats have shown an early perior of severe insomnia lasting several days, followed by a two or three day long recovery to more or less low normal amounts of both REM and NREM sleep. We have also observed a similar pattern of sleep reduction and recovery in two monkeys that we treated with PCPA for several weeks. Accordingly, we may assert that the finding of normal amounts of sleep in schizophrenic patients is no objection to regarding the chronic PCPA cat as a laboratory model of this condition.

The most striking parallelism between patients and PCPA cats in terms of overall sleep patterns can be seen only when we examine schizophrenic data derived from <u>longitudinal</u> studies. Such data is hard to come by because it requires the rarely encountered combination of opportunity and industry. The only good longitudinal data that we have seen was reported by Snyder[48], who showed that the acute onset of a prolonged psychotic episode in a schizophrenic patient was accompanied by severe insomnia of several days' duration followed by a return to more normal amounts of sleep. A representative figure in Snyder's report bears a striking resemblance to Figure 4 in this report, which illustrates the day by day sleep changes in a representative cat.

Although we cannot properly define a value for REM sleep latency when cats are allowed to sleep ad lib with round-the-clock polygraphic monitoring, the measure can be evaluated in cats whose sleep is rigidly scheduled by enforcing wakefulness at all other times with a treadmill[49]. As with human subjects, REM latency in cats is essentially the amount of NREM sleep that intervenes between the first onset of sleep and the onset of the first REM period. In five cats who were placed on a daily schedule of 12 hours on the treadmill (awake) and 12 hours in the recording cage (mostly asleep), the initiation of PCPA treatment was followed by marked reductions in REM latencies that ranged from about 60 percent to as little as 10 percent of the baseline values. Similarly, several studies of schizophrenic patients have noted the unusually early occurrence of first REM periods on certain nights. However, a more systematic evaluation in the recent study of Stern et al.[50] which included data from 56 nights of sleep in eight untreated acute schizophrenics showed a highly significant reduction in mean REM sleep latency as compared to normal control subjects (53.3 min. vs. 93.7 min.).

Finally, without attempting an exhaustive description of data, we will merely assert that chronic PCPA administration in cats increases individual variability in amount of time spent in REM and NREM sleep and this, of course, is the most commonly noted observation among all the studies of sleep in schizophrenics.

2. Dreaming during wakefulness.

There is little doubt that serotonin depletion in the cat has the effect of "releasing" something to occur during wakefulness that ordinarily is confined almost entirely to REM periods. If this something, specifically PGO spike activity, is what triggers or instigates dream experiences, then the PCPA cat might qualify as a waking dreamer. If the actively ill schizophrenic is also a waking dreamer, as some have postulated[1,2,3] then the obvious

parallel may be drawn. However, lest we become too sanguine about this simple metaphorical comparison, we should mention some qualifications. The truth of the matter is that we really do not know enough about the essential phenomenology of either psychosis or dreaming to postulate their fundamental identity with any degree of certainty. As Carney Landis has pointed out, "very few persons have had the opportunity to study an autobiographical account by anyone who has lived through a period of insanity"[51]. In recent years, the psychiatric literature has stressed interpretation and there has been a tendency to ignore the literal meaning of what psychotic persons say about themselves. The same tendency has existed to a somewhat lesser extent with regard to dreaming where, again, we have focused on meaning and interpretation at the expense of understanding the essential quality of the experience, as well as the intricacies and determinants of specified dream content.

A second qualification has to do with the possible consequences of combining, or attempting to combine, waking and dreaming functions. While it may be quite all right to generate a dream experience during sleep, when there is presumably no competition for the perceptual equipment, it might be quite different to inject dream images into the ongoing stream of waking perceptions being generated by sensory inputs from the environment. Some years ago, one of us (WD) proposed a simple model of the neural substrate of dreaming. "During REM sleep, dream images are, in effect, being substituted for retinal stimulation at some point in the stimulus-response process"[52]. A later study by Bizzi and Brooks[53] suggested a unique functional neural change during REM sleep which involved an internally generated input to the visual system at the level of the lateral geniculate nucleus via the pontine reticular formation. Specifically, they found that single shock stimulation at pontine sites from which they were able to record PGO spike activity caused

an evoked response in the LGN, but only during periods of REM sleep. At other times, identical stimuli yielded no response. Thus, an alternative pathway for input to the visual system appeared to open up during REM sleep through which discrete bursts of activity generated by REM sleep mechanisms could be funneled into the perceptual apparatus. At the present time, it is parsimonious to assume that these intrusive stimuli in some way give rise to the perceptual imagery of the dream experience. If this is true, then to experience a waking dream would require that these bursts of activity impinge upon the visual system during periods of wakefulness. The appearance of bursts of REM type of spike activity at geniculate and cortical levels during wakefulness, well documented in the PCPA cat, supports the validity of this argument. However, we cannot presume to know what happens when retinal and pontine inputs collide at the lateral geniculate receptors. Does one or the other, presumably the more intense, win out? Does first one, then the other predominate? Is there a gating mechanism that cannot pass more than one input at a time? The present state of our knowleddge allows us to say almost nothing about these and other possibilities. We can only conclude that if the processes that ordinarily give rise to the normal REM-type dream experience, whatever they may be, were "released" into the waking state, they would not necessarily produce a fullblown dream or hallucination in every instance. Such clearcut perceptual intrusions might require that a certain other conditions be fulfilled, and hallucinatory activity might be intermittent, even though the basic instigators might be continuously present.

A third qualification would involve individual reactions to a waking dream. If such intrusive experiences were to be accepted as "real," therefore constituting psychotic symptoms, they would have to be virtually continuous, allowing an individual no chance for comparative reflection, or,

they could have intruded from the very beginning of life, in which case, the real world would never have been properly learned. It is difficult to imagine what the "world view" of someone would be like if his experience of it had been continually intruded upon by his dreams. Such a defect might not announce itself in an unequivocal manner for many years. The occurrence of intrusive mental processes at all ages, and long before the onset of clinical symptoms, is detailed in at least one autobiographical account[54] by a recovered schizophrenic.

Finally, we must ask what aspects of REM sleep would be the minimum substrate required to generate dream experiences outside of REM periods. This is tantamount to asking for a description of the neurophysiology of the waking dream. Is the crucial process REM sleep, or is it merely something that occurs <u>in</u> REM sleep? It has often been pointed out that the most striking feature of the dreaming brain is its close resemblance to the waking brain[55,56,57]. Studies of many physiological variables during REM sleep uniformly suggest the presence of a high level of arousal, in no way different from that seen during active wakefulness. There are, in fact, only three differences between REM sleep and wakefulness that are worth mentioning - two have been objectified and one has been inferred. Concretely, REM sleep is characterized first by a powerful inhibitory process[58,59,60] which presumably prevents peripheral motor responses to the output of the dreaming brain, thereby maintaining sleep, and second, by the previously described PGO spike activity. The third characteristic is the lack of awareness of the environment - we infer a shutting out of environmental stimuli although evoked potentials can still be easily elicited.

It is our working hypothesis that PGO spike activity, or rather, its human analog (as yet undemonstrated), is the minimum neural substrate of

dream images. The continual occurrence of such activity in the waking state, as exemplified by the PCPA cat (see Figure 3), would not necessarily mean an endless sequence of waking dreams. Rather, it would mean the more or less continual operation of an intrusive process that might produce different things at different times, depending upon what else was going on. Thus, the essential quality of the experiential world produced by administration of PCPA would probably be an unpredictable mixture of externally and internally generated perceptions.

By contrast, the phrase, "dreaming while awake," which might imply a sensorium almost completely dominated by dream images, probably applies more aptly to the "locus coeruleus" preparation of Jouvet and Delorme[61]. Bilateral destruction of this nucleus appears to accomplish a selective disruption of the motor inhibitory process while all other aspects of REM periods are left more or less intact. The result is a cat that goes from wakefulness to NREM sleep in a normal fashion and shows the onset of REM periods at the proper times. These REM periods show normal PGO spike activity, but there is no EMG suppression and behavior, presumably the typical "behavior" of REM sleep, occurs. The locus coeruleus cat is completely oblivious to his environment during these "REM episodes," but he can be "aroused" by moderately intense stimuli in which case the episode is terminated and a period of completely normal wakefulness ensues. Although these two preparations are related, the essential difference between the locus coeruleus cat and the PCPA cat is that in the former, REM sleep intrudes into the waking state, whereas in the latter, something that ordinarily occurs only within REM sleep intrudes into the waking state. The intrusion of PGO spike activity during wakefulness in the PCPA cat is also far more pervasive.

Although we have spoken a great deal about "dreaming" in the cat, we have not yet directly confronted the question of whether or not the cat actually dreams. It is tempting to conclude that the relatively primitive nervous system of the cat lacks the capacity to elaborate complex imagery in response to PGO spikes and let the issue rest. This position would be compatible with the precise nature of the oculomotor activity during REM periods in the cat which, in contrast to the human, does <u>not</u> suggest that the cat is looking at something. Rather, the eye movement typically occurs in intermittent clusters of small, rapid nystagmoid jerks with little or no variation in the plane of movement.

On the other hand, we have accumulated some anecdotal evidence which militates against a categorical denial of the existence of dreaming in the cat. We have noted, on occasion, marked variations in behavior immediately after arousal from a REM period, particularly if the arousal occurs just after the onset of the REM period. For the most part, cats awaken in a casual and unremarkable fashion. However, they occasionally appear very startled and show pilo-erection, pupillary dilation, and other signs of either anger or fear. Since the arousing stimuli are essentially constant, such variation could be due to some unusual "dream" activity in the REM sleep just preceding arousal. The same kind of behavior has been observed with spontaneous arousals on a few occasions. Such evidence certainly does not suggest that the cat dreams throughout every REM period. Rather, it is more compatible with the notion that the PGO spike activity is occasionally intense enough to elicit a complex perceptual response.

By the same token, we are not sure that bursts of PGO spikes during wakefulness in PCPA cats are accompanied by hallucinations. The answer to this

question depends entirely upon what one is willing to infer from the associated behavior of the cat. Our own conclusions were based mainly upon careful scrutiny of the videotape records upon which the PGO spikes and the cats' behavior were simultaneously displayed. In general, behavioral responses were associated with bursts of spikes (see Figure 6), while single spikes had no behavioral correlate at all. By far the most frequent behavioral correlate of spike bursts was a sequence of searching movements of the head and eyes. In other words, the cat looked around. Our current feeling is that the PGO spike activity does not instigate fullblown hallucinations (waking dream images) in the cat. In the first place, the behavior is <u>not</u> ordinarily accompanied by signs of emotion - anger, fear, or affection. In the second place, the animals rarely exhibit visual fixation - rather, the behavior more properly suggests alerting, searching, and/or expectancy. The best inference is that a burst of PGO spikes in the waking state is perceived by the cat as a barrage of simple stimuli, like knocking on a door or flashing a light. Occasionally, the cat does respond to waking spike bursts with behavior that could be termed hallucinatory. However, we are willing to stipulate that although PGO spikes may be a necessary ingredient in the production of hallucinations, they are not sufficient, and that the ability to respond to their occurrence with the elaboration of complex imagery might require more brain than the cat possesses.

Assuming that PGO spikes do exist in the human, we would therefore expect that the most definitive information could only be obtained from a study of PCPA administration with human volunteers. One study has been reported in which patients with malignant carcinoid were treated with PCPA to control the high levels of peripheral serotonin[47]. Although it is uncertain that

an effective depletion of brain serotonin was accomplished, patients receiving the maximum doses developed florid psychotic symptomatology, including hallucinations, which necessitated discontinuation of treatment.

We have obtained additional evidence on this issue from pilot observations on a pair of adult male rhesus monkeys. The monkeys were not implanted for polygraphic recordings, but were observed continuously day and night in their cages during a course of treatment with PCPA at a daily dose of 150-250mg/kg. After about eight to ten days on the drug, both monkeys showed behavior that all observers emphatically agreed was hallucinatory. In other words, both monkeys appeared to be experiencing and responding to internally generated visual images that were projected into the outer world. A representative example of such occurrences involved the stereotyped threat behavior performed by the monkeys whenever the experimenters approached too near the cages. After the PCPA effect had developed, this behavior was often emitted with a definite affective component (recorded on videotape) when no one was in the vicinity.

It would appear that PCPA, through the mechanism of selective depletion of brain serotonin, causes the development of hallucinations or closely related behavioral responses in cats, monkeys, and humans. In cats, the basis of the hallucinatory or searching responses appears to be the occurrence of bursts of PGO spikes in the waking state. It is simply more parsimonious to assume that the same process gives rise to both dreams and hallucinations than to posit two entirely different mechanisms; assuming a single process, it follows that the occurrence of any fullblown hallucinatory experience in the waking state must involve an abnormal discharge of REM events, and the easiest, if not the only way, to accomplish such an abnormal discharge is to interfere with the normal function of serotonergic neurons. That serotonin is

definitely implicated seems absolutely certain. All the serotonin depletors - reserpine, tetrabenazine, para-chloromethamphetamine, PCPA, etc. - bring on an uncontrolled discharge of PGO spikes. Manipulations that directly damage the serotonergic neurons also "release" PGO spikes, as for example, raphe lesions, and a similar intervention, the "split brain stem preparation" of Michel and Roffwarg[62]. No other procedures or pharmacological treatments have yielded a like result.

With regard to the postulated relationship between PGO spikes and dream images, the objection might be raised that while spikes occur in REM sleep, some dreaming is known to take place in NREM sleep. In the first place, substantial numbers of feline PGO spikes actually occur in NREM sleep (see Figures 1 and 2). Secondly, there is now good evidence, obtained by Pivik et al.[63] in our laboratories, that phasic events are discharged in human NREM periods, and by inference, PGO spike activity. Pivik has described a phasic (very brief) suppression of the tonic electromyographic activity during NREM sleep and has noted that a similar suppression may be seen occasionally in cats in association with single or double NREM PGO spikes. Examples of phasic EMG suppressions in both man and cat are shown in Figure 7. In addition to the well-known tonic motor inhibition dissociated with REM sleep, Pompeiano[58] has described a phasic inhibition that comes into play briefly during REM periods in conjunction with spike bursts. The existence of an active phasic motor inhibitory process during NREM sleep in humans has just been demonstrated by Pivik who showed that the electrically elicited "H" reflex was transiently suppressed at the exact moment of the spontaneous EMG suppression. Accordingly, there is a strong inference that activity analogous to the feline PGO spike occurs during NREM sleep in humans and, in line with our postulated

relationship, we may assume that this activity gives rise to NREM dreaming. Obviously, if we grant that PGO spikes occur in NREM sleep in humans, we must also assume their occurrence in REM sleep.

3. The response to selective REM sleep deprivation in PCPA cats.

Although its basic significance is still a puzzle, the existence of the REM sleep deprivation-compensation phenomenon has been conclusively established in a variety of species[64,65,66,67,68]. The simplest explanation for its occurrence has been in terms of some sort of need for REM sleep which requires that it must be at least partially "made up" after any sizable loss. Aside from the very fact of its existence, the assumption that there is a "need" for REM sleep is based almost exclusively on the consistent occurrence of this post-deprivation rebound. When we attempted to get a clearer idea about why REM sleep might be necessary by studying the effect of long-term selective REM deprivation in cats, we found that the procedure produced no impairment whatsoever[69,70]. Although we did find a rather dramatic and characteristic alteration of behavior in REM-deprived cats, a result that we subsequently confirmed in REM-deprived rats[71,72], we were still forced to conclude that cats could dispense with REM sleep for long periods, and suffer only the consequence of an enhanced drive state. This conclusion did not seem compatible with the universal occurrence of REM sleep in adult mammals, nor with its vigorous compensatory response to deprivation. Indeed, the lack of deprivation associated impairment led us to propose that the crucial role of the REM state was fulfilled *in utero*[56] in terms of ensuring maximal activity during a developmental stage when the nervous system is isolated from external sources of stimulation. We also suggested that no important role for REM sleep existed in the adult organism.

In addition, our long-term REM deprivation studies also undermined the notion of an obligatory quota of REM sleep. It was clearly shown that after some duration of deprivation had been accomplished, usually around 20 - 30 days, the cats seemed to achieve some sort of equilibrium where further deprivation yielded no additional change, either in drive-oriented behavior or in the size of the recovery rebound. At the time, it seemed possible that this equilibrium was achieved through the mechanism of an intensity change by which the small amounts of REM sleep that occasionally eluded the deprivation procedure became collectively sufficient to forestall the further accumulation of REM sleep loss. In addition to evidence of an increased frequency of phasic events within the REM fragments, the phasic events were also occurring with a greater intensity in NREM sleep, i.e., just before the onset of REM periods[73]. These changes in intensity in turn suggested the possibility that the presumed obligatory aspect of REM sleep might involve only the phasic events, in particular, the PGO spikes, and that the REM periods might function solely as a time in which maximal discharge of this activity could be achieved without endangering the organism or intruding upon - thereby possibly disrupting - the functions of the waking state.

We recently have tested the functional equivalence of NREM and REM PGO spikes, and also the possibility that the NREM spike discharge provides some reduction of the need for REM periods. Our method was to deprive cats of REM periods plus NREM PGO spikes by arousing them immediately after the occurrence of the first detectable PGO spike in NREM sleep. This procedure was called "spike deprivation." The results showed that the spike deprivation procedure led to a more rapid deprivation effect and a larger REM sleep rebound than the same amount of classical REM sleep deprivation. Conversely,

if we were able to maximize the occurrence of PGO spikes in NREM sleep while at the same time eliminating REM periods, the manipulation would be followed by little or no behavioral change and little or no compensatory REM rebound. These results suggested that the crucial factor in the REM sleep deprivation-compensation phenomenon might actually be the deprivation of PGO spike discharge, and further suggested that REM sleep loss would elicit no rebound if this unique neural discharge were achieved in some alternative manner.

The foregoing results were obviously highly relevant to our consistent findings of rebound failure after selective REM sleep deprivation in actively ill schizophrenic patients, described in an earlier section. The first suggestion was that the lack of REM rebound in the patients was due to enhanced phasic activity at some other time, possibly in NREM sleep periods. We then realized that the postulated discharge was more likely to be occurring during wakefulness, which would explain not only the rebound failures, but the active psychotic symptomatology as well. This line of thought received great impetus when the PGO spike releasing effect of PCPA in cats became known, and a situation that paralleled the postulated daytime phasic event discharge in psychotic patients was hence available for study.

We decided to test the accuracy of our reasoning by REM-depriving chronic PCPA cats. For this study, we concentrated our efforts on cats who were on a sleep-wakefulness (treadmill) schedule analogous to humans. The first step was to REM-deprive the animals for two days by arousals at the onset of each REM period, commencing immediately after the end of the baseline period, and before the PCPA treatment was started. After the initial period of severe insomnia had passed and daily REM sleep time had returned to more normal

amounts and had stabilized (around 10th PCPA day), we repeated the deprivation. Thus, each cat served as its own control with three or four recovery days following each procedure. Two cats survived to be deprived a third time after the withdrawal of PCPA. Figure 8 depicts a typical result in one cat. All cats showed similar results and provided a striking demonstration of yet another parallel between the actively ill schizophrenic and the chronic PCPA cat. It should be noted that a very slight upward adjustment of the rate of spike discharge in wakefulness would have been sufficient to accomodate the activity that would ordinarily have been discharged during REM periods. This is because the total daily REM time in scheduled PCPA cats was around one half to two hours and wakefulness was often as much as 16 & 18 hours. Needless to say, when the animals had recovered from the effects of PCPA to the extent that no PGO spikes were seen during wakefulness, the additional episode of deprivation elicited a substantial REM rebound.

We have results from only one cat, but a striking parallel to the occurrence of exaggerated post-deprivation REM sleep rebounds in remissed schizophrenics should be mentioned. In this experiment, a cat on a 12-hour treadmill - 12-hour recording cage, sleep-wakefulness schedule was deprived of REM periods for two days. At the end of the second deprivation, the PCPA treatment was started. The results are shown in Figure 9. Instead of no REM rebound, an exaggerated REM rebound was observed. This suggested that even before the marked reduction of sleep time and the loss of control or containment of PGO spikes, are seen, an earlier effect of slowly weakening or disrupting the function of the serotonergic neuronal systems is a "loosening up" or partial release of REM sleep itself. Such a mechanism would explain the finding in several cats that values for total REM time on the

first two days of PCPA administration were slightly in excess of the maximum baseline totals. It might also mean that a "sub-clinical" impairment of the serotonergic neurons could be uncovered by an exaggerated response to REM sleep deprivation, which would be a plausible explanation for the exaggerated REM sleep rebounds that were obtained from schizophrenic patients who were without active symptomatology, i.e. in remission[36].

Finally, Snyder[48] has pointed out that a REM deprivation effect does not appear to be a likely factor in the development of an acute schizophrenic psychosis because there is often a drastic reduction of REM sleep time for a few days at the onset of the psychotic episode, but no rebound occurs a few days later when the sleep times return to normal levels. This sequence of events is exactly the same as the changes over time in chronic PCPA cats (see Figure 4), who also show no compensatory rebound when REM times are restored after the initial period of insomnia. The mechanism of these post-insomnia rebound failures is probably the same as has been suggested for the specific REM deprivation studies- a complete release of phasic activity as a result of serotonin depletion so that no need for additional opportunity to discharge accumulates as a result of lost REM sleep.

4. <u>The response of chronic PCPA cats to chlorpromazine (CPZ).</u>

Because the above parallels between actively ill schizophrenics and chronic PCPA cats were so intriguing, we decided to try for yet another.[27] Since the most effective compound for reversing the psychotic state is CPZ or one of its derivatives, we decided to give the drug to five cats who had been receiving 150mg/kg PCPA for 5 to 20 consecutive days. These cats all displayed typical PGO spikes during wakefulness and the reduced fragmented

sleep which accompany the daily administration of PCPA. Two of these cats exhibited compulsive sexual mounting of another male cat while on PCPA.

In every cat, waking spike activity was reduced and long periods of uninterrupted sleep returned after CPZ. This return to baseline-like patterns varied with both the dose of CPZ and the number of days of prior PCPA administration. For example, in one cat who had received PCPA for 8 days and was then given a single 5mg/kg injection of CPZ, the results were dramatic. There was a 90 percent reduction in the number of waking spikes per hour of wakefulness, followed by 42 minutes of continuous sleep. The fall in the number of waking spikes and return of sleep was evident within 30 minutes after the injection and lasted about 36 hours. In cats getting smaller doses of CPZ, the effect was of shorter duration.

One cat was REM deprived before and after CPZ administration while on PCPA. Recovery REM time was not elevated after two days of deprivation while on PCPA alone. However, when deprived only one day and given both PCPA and CPZ, the cat showed a 50 percent increase in REM sleep time on the first recovery day. The two cats in this series who had displayed vigorous mounting of other male cats ceased this behavior temporarily (about 24 hours) after a single dose of CPZ.

Biochemical analysis of the brain of one CPZ treated PCPA cat was done to be sure that CPZ did not reverse the serotonin depletion. No serotonin was detected in any of the brain samples that were assayed.

Thus, in both actively ill schizophrenic patients and chronic PCPA cats, a reversal of abnormal behavior can be achieved by administration of CPZ. In the cat, this reversal is correlated with the return to a normal distribution

of PGO spike discharge. The simplest interpretation would be that CPZ takes over the normal functions of serotonin and/or facilitates the function of any small amounts that might be present.

5. Drive changes in actively ill schizophrenics and chronic PCPA cats.

This is the final parallel we wish to mention, and because it involves areas of behavior that are fraught with difficulties (problems of conceptualization, definition, description, measurement, etc.), we wish only to point it out without making any claim at all as to its promise or authenticity. The real problem, of course, is how to specify or define drive behavior and drive functions in schizophrenic patients. Suffice it to say that the drive functions are surely severely disrupted in one way or another during, and perhaps even before and after, psychotic episodes. As was detailed in an earlier section, by far the most dramatic behavioral changes in PCPA cats were alterations, usually intensifications, in the overt drive oriented behaviors- sexual behavior, eating behavior, aggressive behavior, exploratory behavior, etc. Furthermore, there was marked variability in these behaviors depending upon the duration of serotonin. Thus, the early changes suggested drive enhancement and the later behavior suggested drive depression. In the latter situation, the behavior was easily elicited, but was difficult to sustain.

SUMMARY AND CONCLUSIONS

We have described the effects of chronic PCPA administration in adult cats together with some recent observations on selective REM sleep deprivation in schizophrenic patients. We then attempted to draw significant parallels between actively ill schizophrenics and PCPA cats in the following areas:

1. Similar departures from the normal manifestations of sleep appear to exist in both conditions. A reduction in latency to the first REM period was one of the most obvious changes.

2. It was inferred that REM events intrude into the waking state in both conditions. A large cluster of substantive findings support this inference: although the overall formulation still remains hypothetical.

3. Two days of REM sleep deprivation are <u>not</u> followed by a REM rebound in either actively ill schizophrenics or PCPA cats even when pre-deprivation (baseline) REM times are essentially normal.

4. It appears that CPZ has the capacity to reverse nearly all abnormalities in both conditions.

5. Drive functions are severely and globally disrupted or disturbed in both conditions.

Whether or not these parallels are sufficient justification for regarding the chronic PCPA cat as an animal model of the actively ill schizophrenic was not at issue in this presentation. Rather, in the course of describing experimental results and pointing out certain relationships, we have obtained a clearer notion of the consequences of a presumptive disruption in the functional capacity of serotonergic

neurons in the brain. For example, at the beginning of this presentation we posed the half-serious question, what is it that prevents us from dreaming while we are awake? The effects of prolonged PCPA administration suggest that this is a valid question, and that the answer is a normally functioning serotonin system. This system must also play a role in the normal regulation of sleep and certain behaviors. Thus, it might be reasonable to conclude that sleep research and the study of sleep mechanisms has been and will be a fruitful approach to some of the problems of mental illness. The information presented here plus that which is relevant from other fields such as the neuropharmacology of psychotomimetic compounds may stimulate a more intensive effort to evaluate serotonin functions in schizophrenic patients. Even in the unlikely event that important portions of the psychotic syndromes are proven to be unrelated to dream processes, we can expect that such investigations will yield sufficient clarification of the issue to be well worth the effort.

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Figure 1. PGO spikes: the primary phasic event. The large amplitude, isolated spikes characteristically associated with NREM sleep are shown on the left, while the low amplitude bursts characteristic of REM sleep are shown on the right. The middle tracing shows an intermediate example most typical of the final moments of REM periods, or immediately after the REM onset. Calibrations: 50 microvolts, one second.

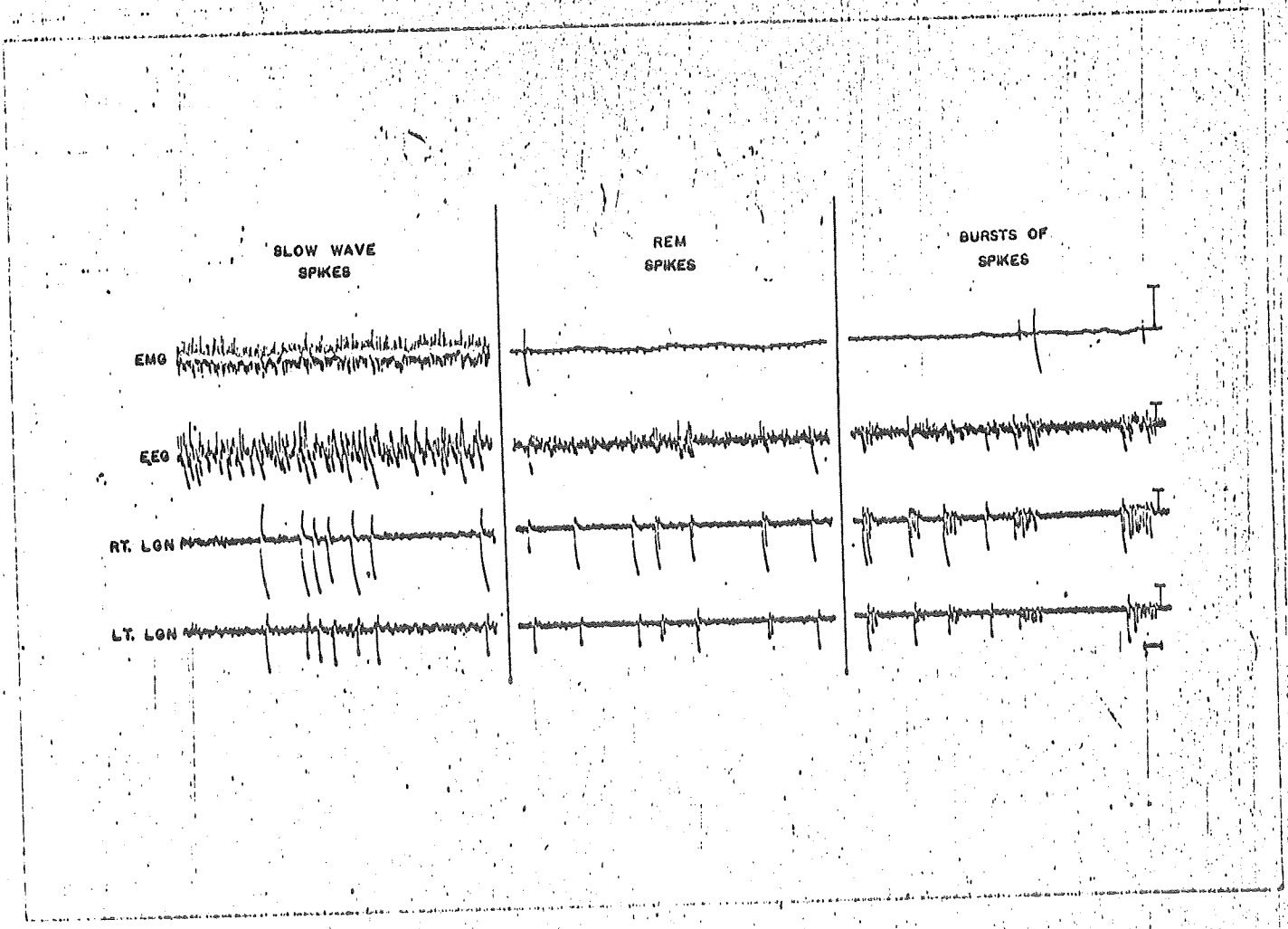


Figure 2. PGO spikes at onset of a REM period in the cat. Derivations: LGN, lateral geniculate nucleus; EMG, electromyogram from posterior neck muscles; EOG, electro-oculogram: CTX, cortical brain waves. Note high amplitude (polarity is irrelevant) single PGO spikes in LGN about 20 seconds before onset of REM period (EMG suppression and EEG activation). Bursts of eye movements and PGO spikes occur simultaneously with EEG activation. EMG suppression is not complete for another few seconds. PGO spikes continue to occur in bursts with or without eye movements for remainder of sample. Calibrations: one second and 50 microvolts.

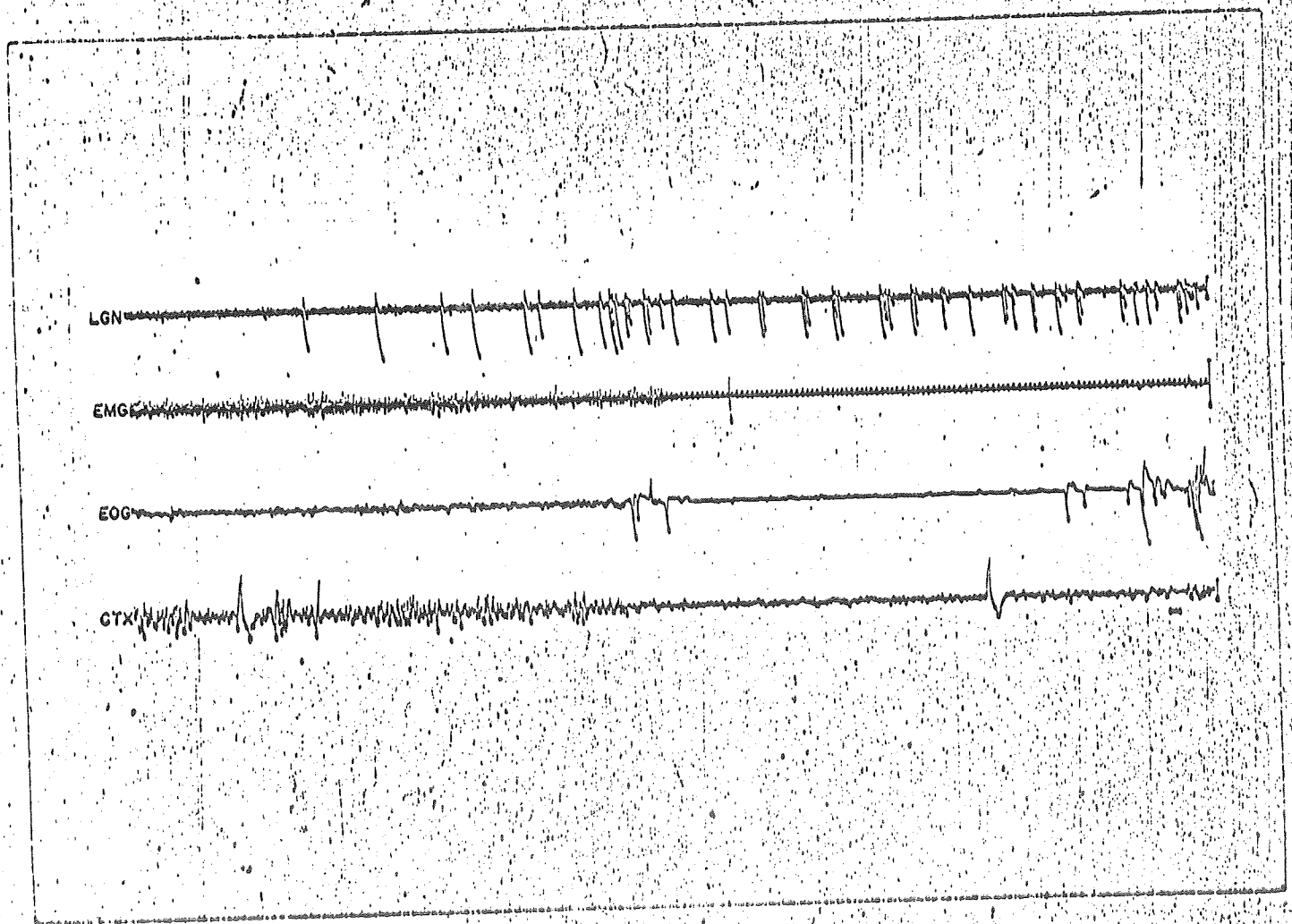
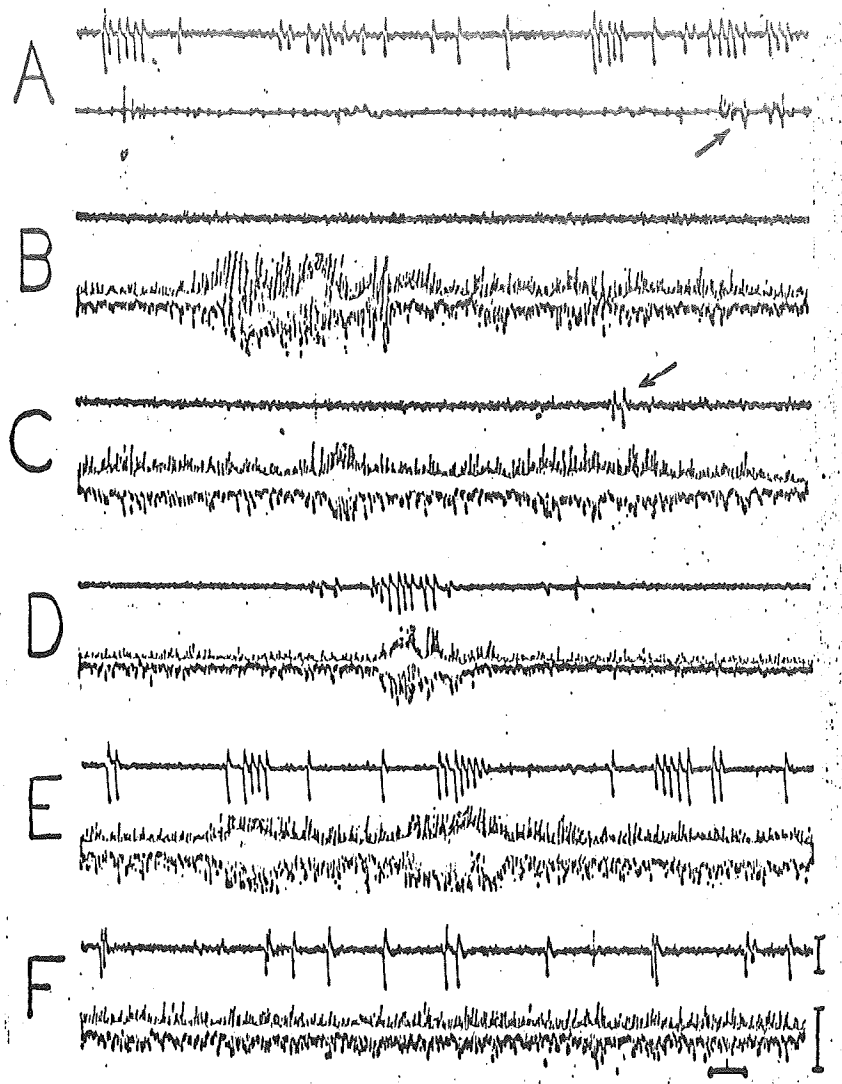


Figure 3. Development of PGO spikes in the waking state during administration of PCPA. All tracings are from the same cat on the same day and were selected from a single four hour time period (0400 to 0800) during which the major changes happened to occur. The top tracing of each pair is a bipolar recording from the left lateral geniculate nucleus (LGN) and the bottom tracing is the simultaneous electromyogram from the posterior neck muscles. Calibrations: 50 uV, 1 sec. A. At 0410, the animal was in a REM period and the sample tracings show the typical PGO spike activity along with the characteristic EMG suppression. There is a miniscule bit of activity toward the end of the EMG sample (arrow) which is concomitant with a flurry of muscular twitching. B. This sample was taken from a period of wakefulness at around 0420. It was exactly like all other recordings seen during wakefulness in a month of continuous baseline observation. The particular LGN derivation shown in these samples remained flat even during body movements. The brief but marked increase of EMG discharge in this tracing indicates gross bodily movement. The overall high level of EMG activity is more or less unique to the waking state. C. At 0437, which was approximately 45 hours after PCPA administration was begun, the first unequivocal PGO spike during wakefulness was seen (arrow). D. The first good burst of spike activity occurred at 0449 and was accompanied by searching movements of the head and eyes (note EMG upsurge). E. By 0630, the PGO spike discharge was virtually continuous and the cat remained fully awake for several hours. F. This sample was selected to illustrate some of the variability in the discharge pattern of PGO spikes. It also shows that a less intense, non-bursting level of PGO spike activity was apparently insufficient for the production of "hallucinatory" behavior. The steady EMG level indicates lack of gross body movement.


A
B
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E
F

Figure 4. Changes in daily amounts of REM sleep and NREM sleep in cat receiving p-chlorophenylalanine (PCPA) and recorded 24 hours per day. All the recordings were carefully scored through a baseline period and 8 consecutive 24 hour periods on the serotonin depleting drug. The daily values for REM and NREM sleep are expressed as per cent of the baseline mean. Note that no significant change occurs on the first two days of PCPA administration except possibly a modest rise in total REM time. On the third PCPA day, there is a precipitous drop in both kinds of sleep which reaches its trough on the fifth day. Essentially normal levels of sleep are achieved by the eighth PCPA day (although still substantially below the baseline values). Brain serotonin is approximately zero at this point suggesting that it is not a crucial agent in the production of either NREM sleep or REM sleep.

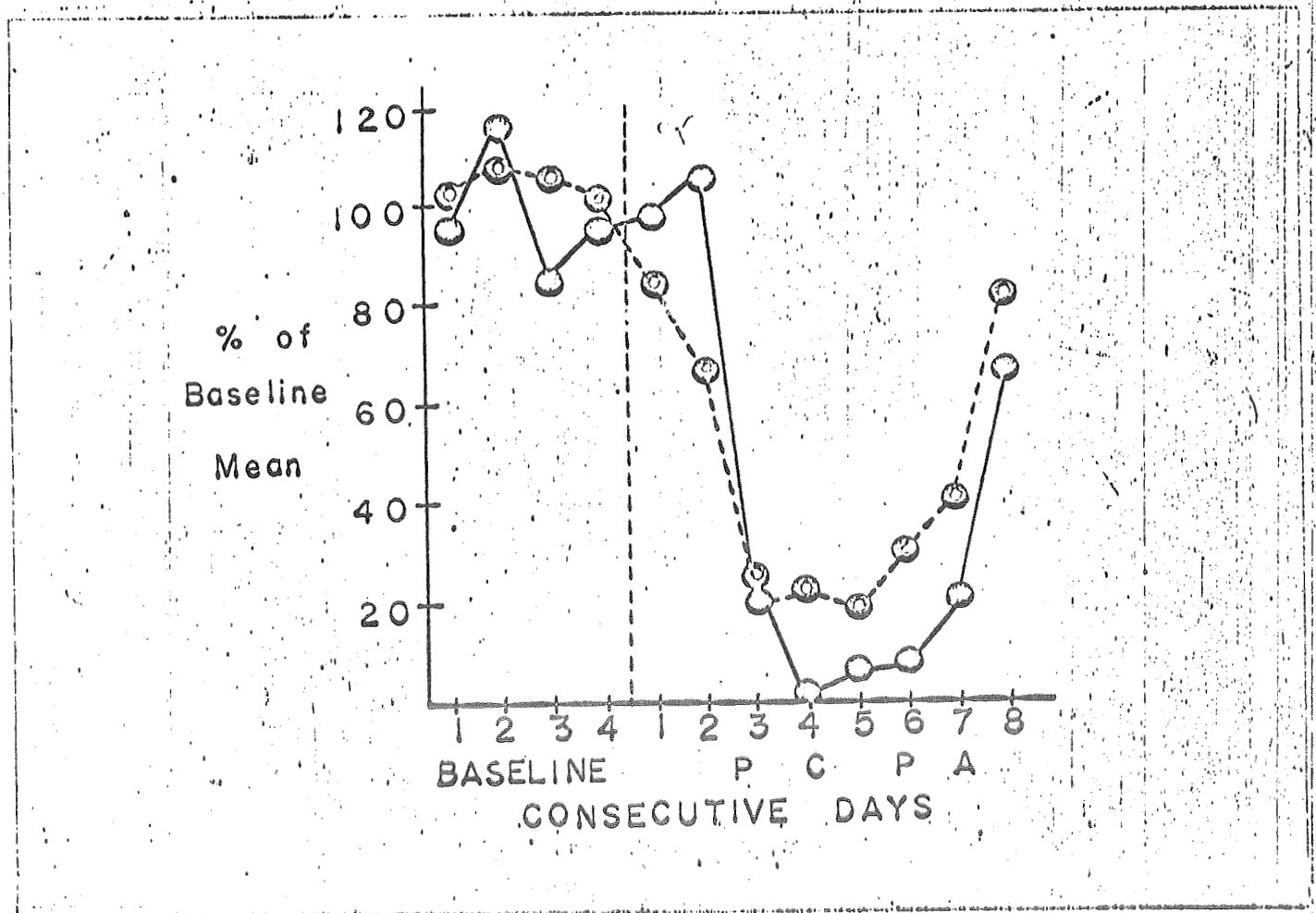

Figure 5. Polygraphic samples from periods of REM sleep before (lower sample) and after (upper sample) treatment with parachlorophenylalanine. LGN, right and left lateral geniculate nuclei; CTX, transcortical recordings from right and left visual cortex; EOG, right and left electro-oculogram; EMG, electromyogram from the posterior neck muscles. The discharge rate of PGO spike activity is about one third normal in the serotonin-depleted cat, although total daily REM time is within normal limits.

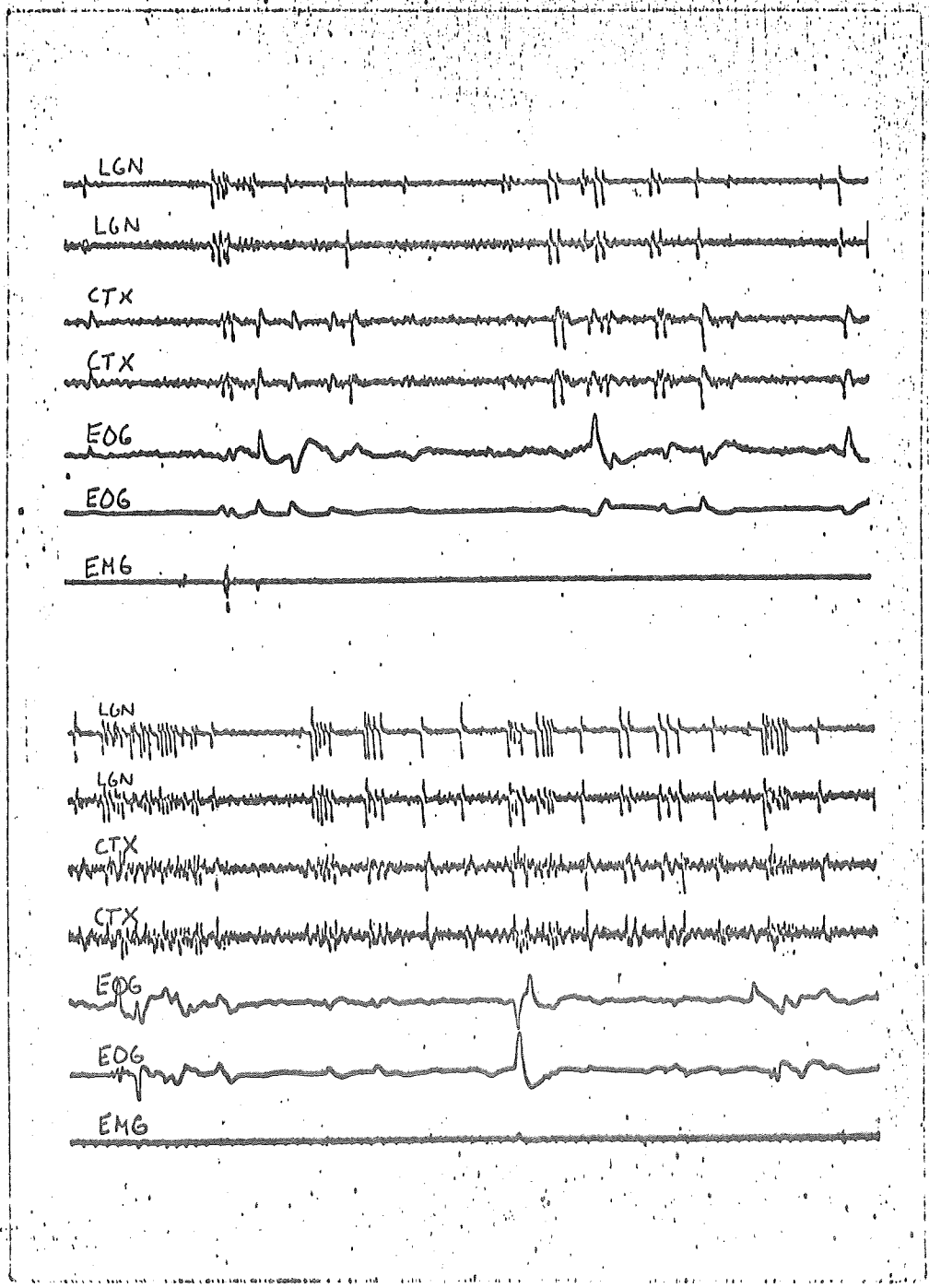

Figure 6. Example of correlative evaluation of "hallucinations" and PGO spike bursts in cat treated with parachlorophenylalanine. LGN, left and right lateral geniculate nuclei; EOG, electro-oculogram from electrodes in vertical (upper tracing) and horizontal planes; CTX, electroencephalogram from left and right visual cortex; EMG, electromyogram from posterior neck muscles; HIPP, dorsal hippocampus. An observer who is watching the cat presses a button which shorts out EMG whenever he judges that cat is "hallucinating." These "hallucinatory" episodes are, most typically, brief periods (about 3 sec in this example) during which the cat looks around in a searching or seeking manner. The lag time between spike burst in the LGN tracings and observer's signal is due to a fairly substantial reaction time which includes, on occasion, a rather complex decision making process.

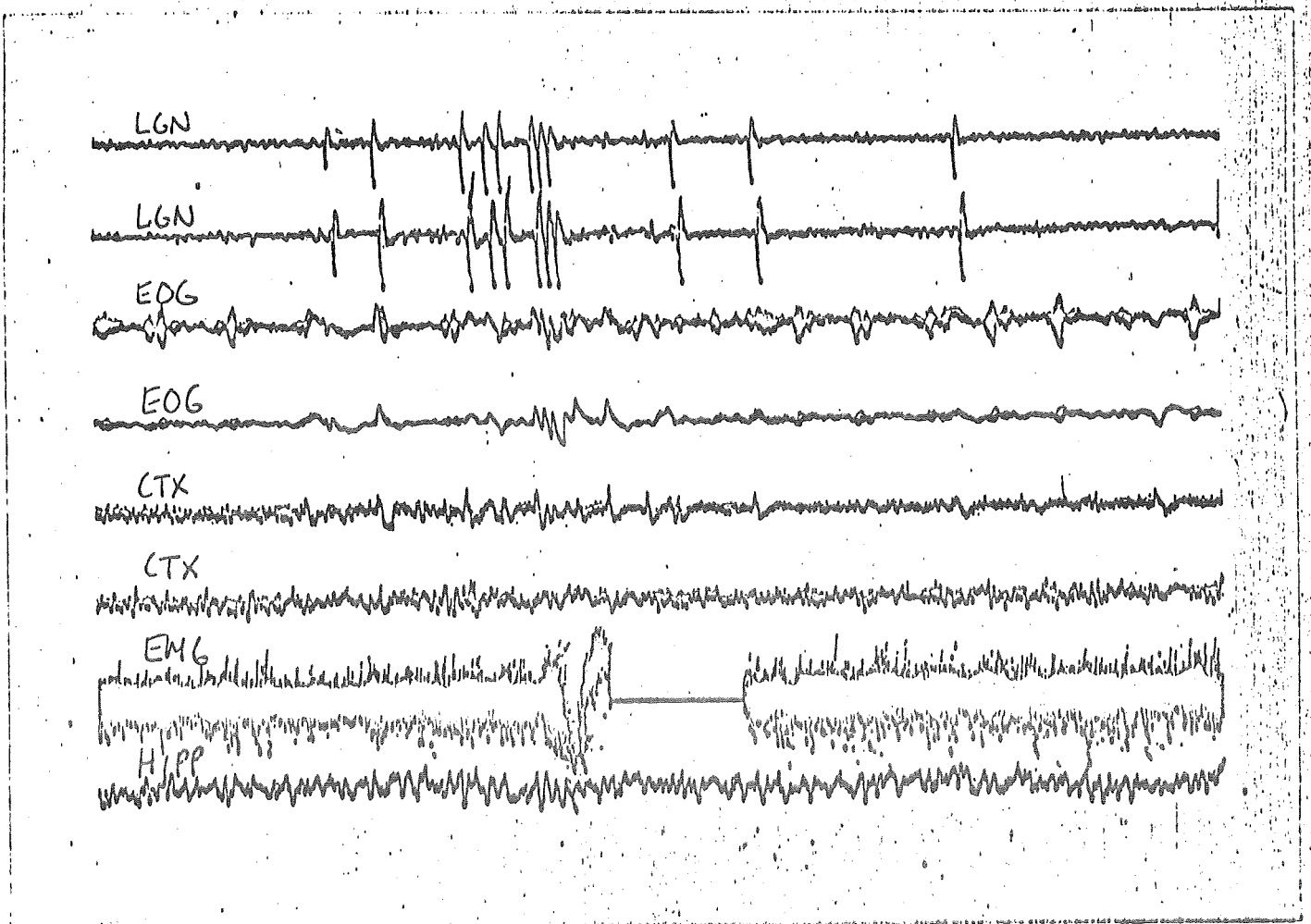

Figure 7. Phasic electromyographic suppressions during NREM sleep in man and cat. EOG, electrooculographic derivations; EEG, brain waves from C3/A2 derivation; CTX, electrocorticogram; LGN, lateral geniculate nucleus; EMG, electromyogram from posterior neck muscles. In the human sample, the suppression (arrow) is closely followed by a "K" complex in the EEG which spreads to the eye leads. In the cat, the EMG suppression is coincident with two spikes in the lateral geniculate nucleus. Calibration: 1 second.

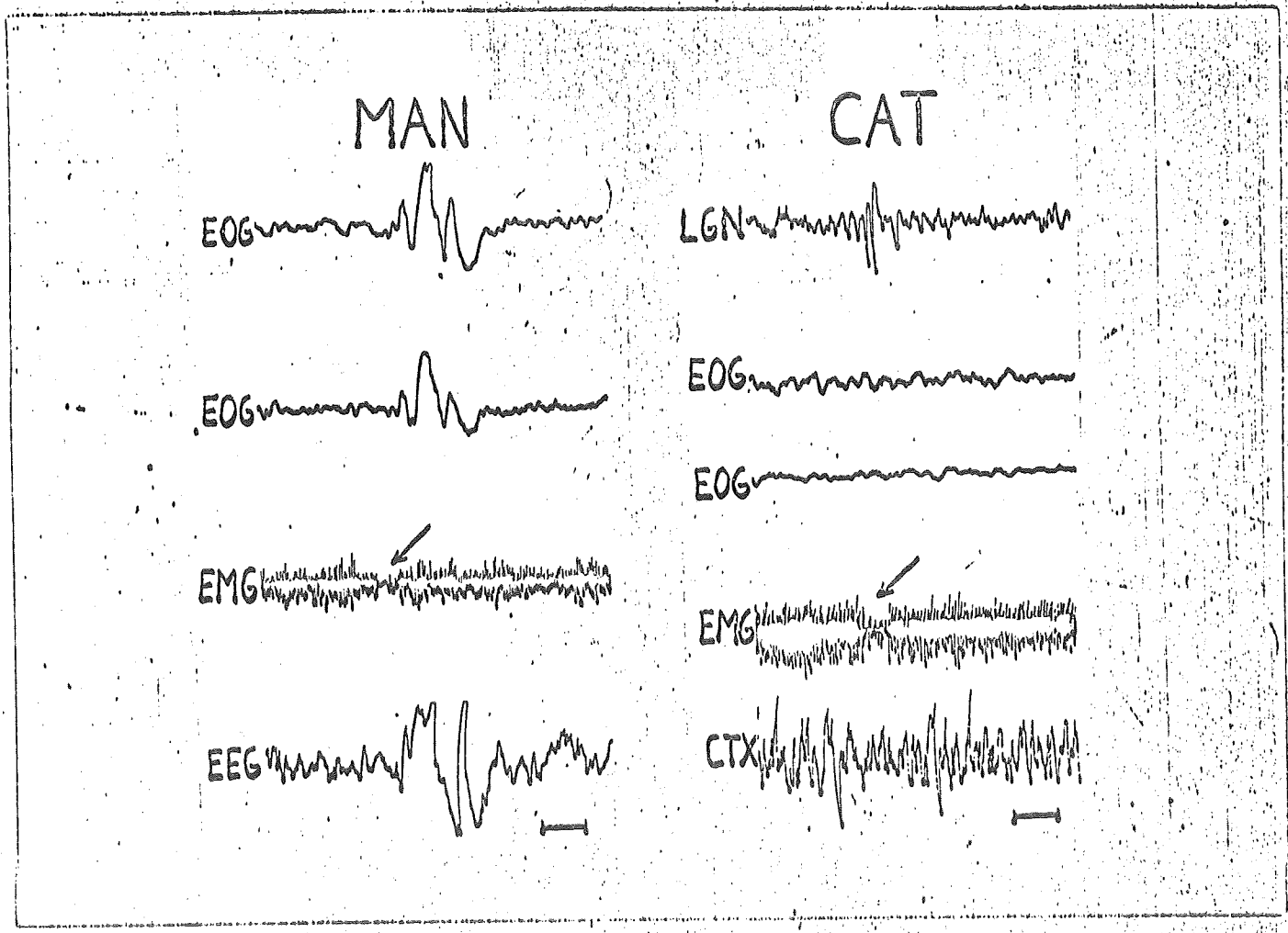

Figure 8. Rebound failure in a cat chronically treated with p-chlorophenylalanine (PCPA). The daily REM time values in this cat during the two deprivation periods are expressed in per cent of the baseline REM sleep time. Since there is usually a small reduction in the daily REM time after an animal has been stabilized on PCPA, 100 per cent of baseline actually represents a different value in the PCPA condition versus the control condition. These values are indicated on the graph in hours and minutes. As can be seen, although this cat was averaging 2 hours, 20 minutes of REM sleep per day on a 12-12 schedule (12 hours on treadmill-12 hours in recording cage) in the PCPA condition, two days of deprivation resulted in no makeup at all. The REM rebound following the similar period of deprivation prior to the administration of PCPA was of normal size. The failure to rebound while on PCPA is to all intents and purposes an exact duplication of the results of REM sleep deprivation in actively ill schizophrenic patients. It is possible that the chronic PCPA animal may serve as a useful model of the actively psychotic condition in humans.

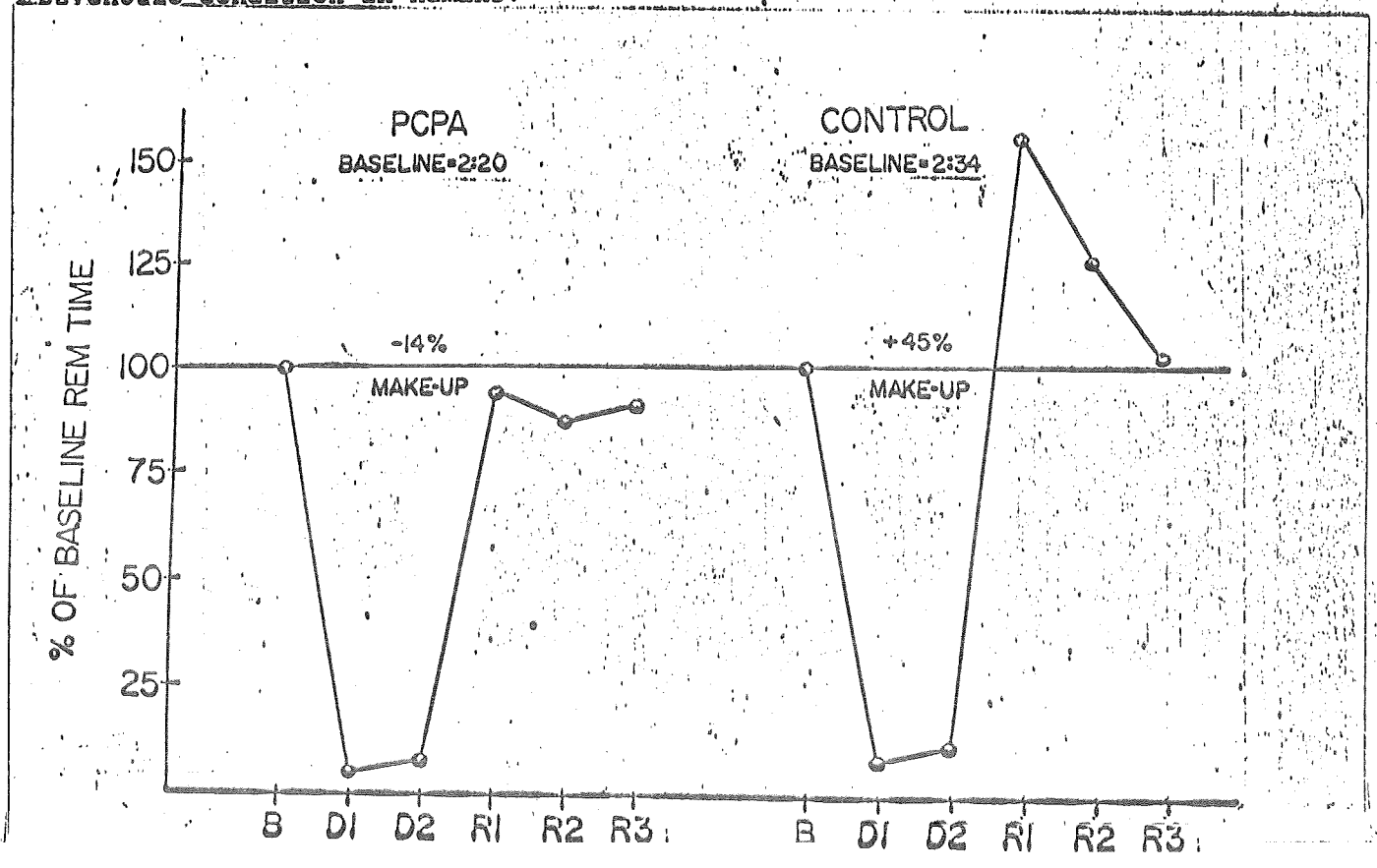

Figure 9. Unusually high REM rebound associated with the initiation of the PCPA treatment in one cat. This animal spent 12 hours each day on a treadmill throughout the study and slept ad lib. in his recording cage during the other 12. The first dose of PCPA was administered immediately after the second deprivation recording period. Twelve hours later, the animal started on his first day of uninterrupted recovery sleep, during which REM time was 69 percent above the baseline mean, a very respectable but not unique amount. However, the second recovery day was completely unique in that the REM sleep level was still strikingly elevated. By recovery day 3, the fullblown PCPA effect with waking PGO spikes and insomnia had emerged, which also affected total REM time. In spite of this, the "extra" REM sleep on the first two recovery days was nearly twice as great as the 3rd day rebound that typically follows two days of deprivation in cats. Therefore, the value on this 3rd day was not included in the "makeup" calculation. On the abscissa, B stands for baseline; D for deprivation; and R for recovery.